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REMARKS

Rejection of Claims 5-34 and 55-57 Under 35 U.S.C. § 112, Second Paragraph

Claims 5-34 and 55-57 have been rejected under 35 U.S.C. § 112, second paragraph, as the Examiner has said that the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 is said to be indefinite for the recitation of "effective amount." It is said that there are no metes and bounds for "effective amount." An "effective amount" does not require quantitative recitations in the claim, but is to be determined by one of ordinary skill in the art who looks to the specification. Applicants have described a number of disorders for which oxygen limitation is indicated. See, for example, page 5, lines 7-19. See also page 24, line 20 to page 25, line 18, and page 28, line 23 to page 30, line 3. One of ordinary skill in the art would be able to decide whether systemic or local administration of a hemoprotein would be appropriate, and determine, without undue experimentation, an appropriate dose to observe an alleviation of the disorder.

Claim 15 is said to be indefinite for the recitation of "prostatic hypertrophy or restenosis." Both conditions recited in Claim 15, prostatic hypertrophy and restenosis, are characterized by proliferation of cells.

See the enclosed Exhibit A (definition of *benign prostatic hyperplasia* in the *Merriam-Webster Medical Dictionary*, 2003, obtained through MedlinePlus® on line), wherein it is seen that *benign prostatic hyperplasia* is the same as *benign prostatic hypertrophy*. It is true that in one definition, *hypertrophy* can involve an enlargement of cells. However, that is only one definition of several listed, and in other definitions appropriate to this case, *hypertrophy* means *hyperplasia*, a multiplication of cells. See also Exhibit B (definition of *hyperplasia* in *Dorland's Illustrated Medical Dictionary*, 27th Edition, W.B. Saunders Company, Philadelphia, 1988).

See the enclosed Exhibit C (pp. 1412 and 1378 of *Harrison's Principles of Internal Medicine*, 15th Edition, Braunwald *et al.*, eds., McGraw-Hill, New York, 2001). The top of the second column of page 1412 describes restenosis as a phenomenon resulting from the proliferation of intimal cells. See page 1378 for an illustration of an artery and a description of

the initiation of atherosclerosis, resulting in stenosis. Also see Exhibit D, definition of *intima* in the *Merriam-Webster Medical Dictionary*, 2003, obtained through MedlinePlus® on line.

Both prostatic hypertrophy and restenosis are conditions of pathologically proliferating cells. Therefore, Claim 15 is properly dependent on Claim 13, and is not indefinite.

Rejection of Claims 1-34, 44 and 55-57 Under 35 U.S.C. § 112, First Paragraph

Claims 1-34, 44 and 55-57 have been rejected under 35 U.S.C. § 112, first paragraph, as they are said to not comply with the enablement requirement.

Applicants have developed methods for in vivo use of a family of hemoproteins with related activities. The hemoproteins are known and have been purified previously. Applicants have thoroughly characterized the activities of these hemoproteins. Applicants do not find any instances where a rejection is proper because ". . . a statement is, on its face, contrary to generally accepted scientific principles." (*In re Marzocchi*, 169 USPQ 367 (CCPA 1971). The activities of the hemoproteins under a variety of circumstances have been characterized and are described in the specification.

Guidance on the in vivo applications of hemoproteins is provided on page 32, line 4 to page 35, line 23 of the specification. Example 5, at page 52, line 1 to page 53, line 10 provides guidance on methods of using hemoprotein to reduce the concentration of NO. The organ culture model of rabbit aortic ring segments has been used extensively to show the effects of drugs, enzymes, etc. on the NO concentration, and thus, for example, on blood pressure.

The conditions used in Example 5 can be used as a starting point by one of ordinary skill in the art to adjust dosages applicable to a particular medical condition. Further experiments can be done by those of skill in the art to optimize conditions for hemoprotein therapy to reduce concentrations of NO and reverse hypotension. See, for example, page 55, lines 3-14, which would not involve undue experimentation for a person skilled in the art.

Rejection of Claim 45 Under 35 U.S.C. § 112, First Paragraph

Claim 45 has been rejected under 35 U.S.C. § 112, first paragraph, as the specification is said to not enable any person skilled in the art to make and/or use the invention commensurate in scope with the claim.

Guidance on the in vivo administration of hemoproteins to reduce blood flow to tumors can be found in the study described on page 53, line 11 to page 54, line 9. The result of this study was that NO dioxygenase IV reduced tumor blood flow. Further details of an anti-tumor regimen can be determined after experiments of the type described on page 55, line 15 to page 56, line 2. The description of the experiment is sufficient guidance for one of ordinary skill in the art to carry out studies to optimize treatment regimens for the inhibition of blood flow in a tumor, without undue experimentation.

Mouse mammary adenocarcinoma is a commonly used model for the study of the effects of treatments on tumor growth. This model is accepted as such by persons of ordinary skill in the art as predictive of similar results with other types of tumors in other mammals, including humans.

CONCLUSION

The Examiner is requested to consider the above remarks, and withdraw the rejections. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

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Medical Dictionary

4 entries found for **hypertrophy**. Select an entry and then click 'Go'.

hypertrophy[1,noun]
hypertrophy[2,intransitive verb]
benign prostatic hyperplasia
eccentric hypertrophy

Go

Main Entry: **benign prostatic hyperplasia**
Function: *noun*
: adenomatous hyperplasia of the periurethral part of the prostate gland that occurs especially in men over 50 years old and that tends to obstruct urination by constricting the urethra -- abbreviation *BPH*; called also *benign prostatic hypertrophy*

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Pronunciation Key

\&\ as a and u in abut	\ch\ as ch in chin	\o\ as aw in law
\ᵊ\ as e in kitten	\e\ as e in bet	\oi\ as oy in boy
\&r\ as ur and er in further	\E\ as ea in easy	\th\ as th in thin
\a\ as a in ash	\g\ as g in go	\t͟h\ as th in the
\A\ as a in ace	\i\ as i in hit	\ü\ as oo in loot
\ä\ as o in mop	\I\ as i in ice	\u\ as oo in foot
\au\ as ou in out	\j\ as j in job	\y\ as y in yet
	\[ng]\ as ng in sing	\zh\ as si in vision
	\O\ as o in go	

EXHIBIT
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A

27th Edition

DORLAND'S ILLUSTRATED

Medical Dictionary

W.B. SAUNDERS COMPANY
Harcourt Brace Jovanovich, Inc.
Philadelphia London Toronto
Montreal Sydney Tokyo

Dorland's illustrated medical dictionary.
Philadelphia: W.B. Saunders Co.,
v.: ill.; 27 cm.
Irregular.
Began publication with 23rd ed.
Description based on: 26th ed.
Continues: American illustrated medical dictionary.

1. Medicine—Dictionaries. I. Dorland, W.A. Newman (William Alexander Newman), 1864–1956.
[DNLM: 1. Dictionaries, Medical. 2. Reference Books, Medical]

R121.D73 610'.3'21—dc19 0-6383
AACR 2 MARC-S

Library of Congress [8607r85]rev6

W.B. SAUNDERS COMPANY
Harcourt Brace Jovanovich, Inc.
The Curtis Center
Independence Square West
Philadelphia, PA 19106

Listed here are the latest translated editions of this book together with the languages for the translations and the publishers.

Italian *(26th Edition, revised)*—Edizioni Scientifiche Internazionali (ESI), Milan, Italy

Japanese *(26th Edition)*—Hirokawa Publishing Company, Tokyo, Japan

Spanish *(26th Edition)* (Adaption)—Nueva Editorial Interamericana, Mexico City, Mexico

Managing Editor, Dictionaries: Elizabeth J. Taylor
Editors: Douglas M. Anderson, Joseph M. Patwell, Katharine Plaut, Kathleen McCullough
Production Manager: Carolyn Naylor
Illustrator: Sharon Iwanczuk
Illustration Coordinator: Walt Verbitski
Mechanical Artist: Melissa Walter

Dorland's Illustrated Medical Dictionary ISBN 0-7216-3154-1

Library of Congress catalog card number 78–50050

Last digit is the print number: 9 8 7 6 5

hyperpexia (hi″per-pek′se-ah) [*hyper-* + Gr. *pēxis* fixation + *-ia*] fixation of an excessive amount of a substance by a tissue.

hyperpexy (hi″per-pek′se) hyperpexia.

hyperphagia (hi″per-fa′je-ah) [*hyper-* + Gr. *phagein* to eat] ingestion of a greater than optimal quantity of food.

hyperphalangia (hi″per-fah-lan′je-ah) presence of more than the normal number of phalanges in the longitudinal axis of a digit.

hyperphalangism (hi″per-fah-lan′jizm) hyperphalangia.

hyperphenylalaninemia (hi″per-fen″il-al″ah-nĭ-ne′me-ah) a group of genetic aminoacidopathies due to the impaired hydroxylation of phenylalanine to tyrosine by defective phenylalanine hydroxylase; there is an accumulation of phenylalanine with increased shunting of its metabolities. There are eight types of hyperphenylalaninemia based on biochemical defect: *type I* is classic phenylketonuria (q.v.); *type II* or *persistent hyperphenylalaninemia* and *type III* or *transient mild hyperphenylalaninemia* are usually clinically normal; *type IV* or *dihydropteridine reductase deficiency* or *malignant hyperphenylalaninemia* or *phenylketonuria II,* and *type V* or *dihydrobiopterin synthetase deficiency* or *atypical phenylketonuria* or *phenylketonuria III* show clinical manifestations in the first year of life, with severe neurologic damage; *type VI* or *persistent hyperphenylalaninemia and tyrosinemia* shows progressive ataxia and seizures during the second year of life; *type VII* or *neonatal tyrosinemia* (q.v.) is the only X-linked form; and *type VIII* is hereditary tyrosinemia (q.v.). Called also *phenylalaninemia.* **malignant h.,** hyperphenylalaninemia, type IV.

hyperphonesis (hi″per-fo-ne′sis) [*hyper-* + Gr. *phōnēsis* sounding] an increase in intensity of the vocal sound in auscultation, or of the percussion note.

hyperphonia (hi″per-fo′ne-ah) [*hyper-* + Gr. *phōnē* voice] excessively energetic phonation, as in stuttering.

hyperphoria (hi″per-fo′re-ah) [*hyper-* + *phoria*] a form of heterophoria in which there is permanent upward deviation of the visual axis of an eye after the visual fusional stimulus has been eliminated.

hyperphosphatasemia (hi″per-fos″fah-ta-se′me-ah) high levels of alkaline phosphatase in the blood. **chronic congenital idiopathic h.,** hyperostosis corticalis deformans juvenilis. **h. tar′da,** hyperostosis corticalis generalisata.

hyperphosphatasia (hi″per-fos″fah-ta′ze-ah) hyperphosphatasemia.

hyperphosphatemia (hi″per-fos″fah-te′me-ah) an excessive amount of phosphates in the blood; it is usually asymptomatic.

hyperphosphaturia (hi″per-fos″fah-tu′re-ah) an excessive amount of phosphates in the urine.

hyperphosphoremia (hi″per-fos″fo-re′me-ah) an excessive amount of phosphorus compounds in the blood.

hyperphrenia (hi″per-fre′ne-ah) [*hyper-* + Gr. *phrēn* mind] 1. great mental excitement. 2. excessive mental activity.

hyperpigmentation (hi″per-pig″men-ta′shun) abnormally increased pigmentation.

hyperpinealism (hi″per-pi′ne-al-izm) abnormally increased activity of the pineal body.

hyperpituitarism (hi″per-pĭ-tu′ĭ-tah-rizm″) a condition due to pathologically increased secretion of pituitary hormones resulting from functioning adenomas producing growth hormone (resulting in acromegaly, pituitary gigantism), corticotropin (resulting in Cushing's disease), or prolactin (resulting in galactorrhea-amenorrhea syndrome).

hyperplasia (hi″per-pla′ze-ah) [*hyper-* + Gr. *plasis* formation] the abnormal multiplication or increase in the number of normal cells in normal arrangement in a tissue. Cf. *hypertrophy.* **adrenal cortical h.,** hyperplasia of adrenal cortical cells, as in adrenogenital syndrome and Cushing's syndrome. **angiolymphoid h.,** one or more erythematous dermal or subcutaneous nodules occurring primarily on the head and neck of young adults, sometimes associated with lymphadenopathy and peripheral eosinophilia. The more superficial, usually larger, lesions have been called *pseudopyogenic granuloma.* Called also *Kimura disease.* **cementum h.,** hypercementosis. **chronic perforating pulp h.,** internal tooth resorption (def. 1). **congenital adrenal h.,** adrenogenital syndrome. **congenital virilizing adrenal h.,** adrenogenital syndrome. **cutaneous lymphoid h.,** a term for several benign cutaneous disorders with lesions clinically and histologically resembling those of malignant lymphoma. The lesions may be lymphoreticular, granulomatous, and follicular and include lymphocytes, histiocytes, eosinophils, plasma cells, and lymphoid follicles. The disorders may be of unknown etiology or be reactions to insect bites, allergy hyposensitization injections, light, trauma, and tattoo pigment. The term embraces lymphocytoma cutis, lymphadenosis benigna cutis, Spiegler-Frendt sarcoid, lymphocytic infiltration of the skin, and insect bite granuloma. Called also *cutaneous lymphoplasia.* **Dilantin h.,** see under *gingivitis.* **endometrial h., h. endome′trii,** abnormal overgrowth of the endometrium. **fibrous inflammatory h.,** masses of collagenized, fibrous connective tissue along the borders of ill-fitting dentures or in other areas where chronic irritation exists. Called also *epulis fissuratum.* **giant follicular h.,** a disorder of the lymph nodes, generally confined to the cervical lymph nodes, which may simulate follicular lymphoma, but cytologically the follicles contain both macrophages and lymphoblasts. **gingival h.,** noninflammatory enlargement of the gingivae produced by factors other than local irritation. See also under *enlargement.* **inflammatory h.,** hyperplasia brought about by inflammation. **juxtaglomerular cell h.,** a syndrome in which hypertrophy and hyperplasia of juxtaglomerular cells produces hypokalemic alkalosis and hyperaldosteronism; it is characterized by absence of hypertension in the presence of markedly increased plasma renin concentrations, and by insensitivity to the pressor effects of angiotensin. It usually affects children, may be autosomal recessive, and may be associated with other anomalies, such as mental retardation and short stature. Called also *Bartter's syndrome.* **lipoid h.,** increased formation of lipoid-containing cells. **neoplastic h.,** hyperplasia brought about by a new growth. **nodular lymphoid h.,** a proliferation of small nodules of lymphoid tissue, seen in the terminal ileum and colon of children, in the small intestine and sometimes colon and stomach of adults with primary immunodeficiency disease, and, rarely, in the small intestine of adults with malignant lymphoma. **ovarian stromal h.,** thecomatosis. **polar h.,** excessive development at either extremity of the embryo, producing a monster either with two heads or with three or more lower limbs. **pseudoepitheliomatous h.,** a benign proliferative epithelial hyperplasia, the cytoarchitectural features of which are suggestive of squamous cell carcinoma; occurring in certain inflammatory diseases, especially granulomatous reactions and ulcerations. **Swiss-cheese h.,** hyperplasia of a tissue which on section shows openings as in Swiss cheese.

hyperplasmia (hi″per-plaz′me-ah) [*hyper-* + *plasma*] 1. excess in the proportion of blood plasm to corpuscles. 2. abnormally large size of erythrocytes through the absorption of plasma.

hyperplastic (hi″per-plas′tik) pertaining to or characterized by hyperplasia.

hyperploid (hi′per-ploid) [*hyper-* + *-ploid*] 1. having more than the typical number of chromosomes in unbalanced sets, as in Down's syndrome. 2. an individual or cell having more than the typical number of chromosomes in unbalanced sets.

hyperploidy (hi″per-ploi′de) the state of being hyperploid. Cf. *aneuploidy.*

hyperpnea (hi″perp-ne′ah) [*hyper-* + Gr. *pnoia* breath] abnormal increase in the depth and rate of the respiratory movements.

hyperpneic (hi″perp-ne′ik) pertaining to or characterized by hyperpnea.

hyperpolarization (hi″per-po″lar-i-za′shun) any increase in the amount of electrical charge separated by the cell membrane and hence in the strength of the transmembrane potential.

hyperpolypeptidemia (hi″per-pol″e-pep″tĭ-de′me-ah) excess of polypeptides in the blood.

hyperponesis (hi″per-po-ne′sis) [*hyper-* + Gr. *ponesis* toil, exertion] dysponesis in which there is excessive action-potential output from the motor and premotor areas of the cortex.

hyperponetic (hi″per-po-net′ik) pertaining to or characterized by hyperponesis.

HAMILTON, BROOK, SMITH, & REYNOLDS

HARRISON'S 15TH EDITION

PRINCIPLES OF INTERNAL MEDICINE

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MEDICAL PUBLISHING DIVISION

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Harrison's
PRINCIPLES OF INTERNAL MEDICINE
Fifteenth Edition

234567890 DOWDOW 098765432
ISBN 0-07-007272-8 (Combo)
0-07-007273-6 (Vol. 1)
0-07-007274-4 (Vol. 2)
0-07-913686-9 (Set)

FOREIGN LANGUAGE EDITIONS
Arabic (Thirteenth Edition)—McGraw-Hill Libri Italia srl (est. 1996)
Chinese (Twelfth Edition)—McGraw-Hill Book Company—Singapore © 1994
Croatian (Thirteenth Edition)—Placebo, Split, Croatia
French (Fourteenth Edition)—McGraw-Hill Publishing Co., Maidenhead, UK © 1999
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Greek (Fourteenth Edition)—Parissianos, Athens, Greece © 2000
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Japanese (Eleventh Edition)—Hirokawa © 1991
Polish (Fourteenth Edition)—Czelej Publishing Company, Lubin, Poland (est. 2000)
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Romania (Fourteenth Edition)—Teora Publishers, Bucharest, Romania (est. 2000)
Spanish (Fourteenth Edition)—McGraw-Hill Interamericana de Espana, Madrid © 1998
Turkish (Thirteenth Edition)—McGraw-Hill Libri Italia srl (est. 1996)

This book was set in Times Roman by Progressive Information Technologies. The editors were Martin Wonsiewicz and Mariapaz Ramos Englis. The production director was Robert Laffler. The index was prepared by Irving C. Tullar. The text and cover designer was Marsha Cohen/Parallelogram Graphics.

R. R. Donnelley and Sons, Inc. was the printer and binder.

Library of Congress Cataloging-in-Publication Data

Harrison's principles of internal medicine—15th ed./editors, Eugene Braunwald . . . [et al.]. p. cm.
Includes bibliographical references and index.
ISBN 0-07-913686-9 (set)—ISBN 0-07-007273-6 (v. 1)—ISBN 0-07-007274-4 (v. 2)
1. Internal medicine. I. Braunwald, Eugene, date
RC46.H333 2001
616—dc21

00-063809

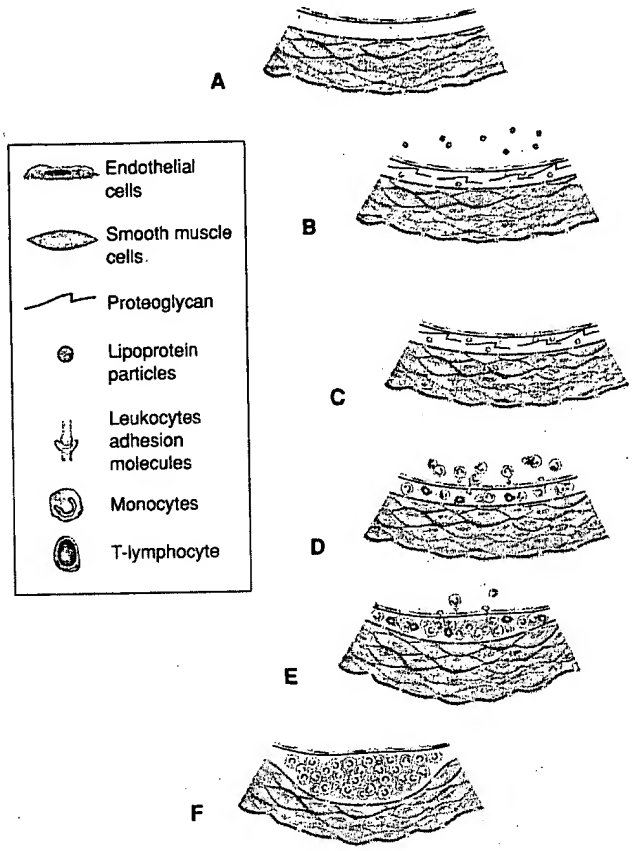

FIGURE 241-1 *A*. The normal artery. The normal artery consists of three layers. The intima, lined by a monolayer of endothelial cells in contact with the blood, contains resident smooth-muscle cells embedded in extracellular matrix. The internal elastic lamina forms the border of the intima with the underlying tunica media. The media contains layers of smooth-muscle cells invested with a collagen- and elastin-rich extracellular matrix. Elastic arteries such as the aorta contain concentric lamellae of smooth-muscle cells sandwiched between dense bands of elastin. Muscular arteries have a looser organization of smooth-muscle cells dispersed within the matrix. The external elastic lamina forms the border of the media with the adventitia. The adventitia contains nerves and some mast cells and is the origin of the vasa vasorum which supply blood to the outer two-thirds of the tunica media.

B. Accumulation of lipoprotein particles. Lipoprotein particles can accumulate in the intima of arteries, particularly when the ambient concentration is increased by hypercholesterolemic states. The lipoprotein particles often associate with constituents of the extracellular matrix, notably proteoglycans. Sequestration within the intima separates lipoproteins from some plasma antioxidants and can favor oxidative modification. Such modified lipoprotein particles may trigger a local inflammatory response responsible for signaling subsequent steps in lesion formation.

C. Adhesion of leukocytes. In hypercholesterolemia, adhesion of mononuclear leukocytes to the luminal endothelial occurs early. The augmented expression of various adhesion molecules for leukocytes probably triggers the first step in the recruitment of white blood cells to the site of a nascent arterial lesion.

D. Penetration of leukocytes. Once adherent, some white blood cells will migrate into the intima. The directed migration of leukocytes probably depends on chemoattractant factors including modified lipoprotein particles themselves and chemoattractant cytokines such as the chemokine macrophage chemoattractant protein 1 produced by vascular wall cells in response to modified lipoproteins.

E. Accumulation of leukocytes. Leukocytes resident in the evolving fatty streak can divide and exhibit augmented expression of receptors for modified lipoproteins (scavenger receptors). These mononuclear phagocytes imbibe lipids and transform into foam cells whose cytoplasm is filled with lipid droplets.

F. Formation of the fibrous cap and lipid core. As the fatty streak evolves into a more complicated atherosclerotic lesion, smooth-muscle cells accumulate within the expanding intima and the amount of extracellular matrix increases. The fibrous cap, formed of extracellular matrix elaborated by the smooth-muscle cells in the intima, characteristically overlies a lipid core filled with macrophages. In addition to dividing, these cells in the lipid core can die, releasing their lipid contents into the extracellular space.

Atherosclerosis manifests itself focally not only in space, as just described, but in time as well. Atherogenesis in humans typically occurs over a period of many years, usually many decades. Growth of atherosclerotic plaques probably does not occur in a smooth linear fashion, but rather discontinuously, with periods of relative quiescence punctuated by periods of rapid evolution. After a generally prolonged "silent" period, atherosclerosis may become clinically manifest. The clinical expressions of atherosclerosis may be chronic, as in the development of stable, effort-induced angina pectoris or of predictable and reproducible intermittent claudication. Alternatively, a much more dramatic acute clinical event, such as myocardial infarction, a cerebrovascular accident, or sudden cardiac death, may first herald the presence of atherosclerosis. Other individuals may never experience clinical manifestations of arterial disease despite the presence of widespread atherosclerosis demonstrated post mortem.

INITIATION OF ATHEROSCLEROSIS **Lipoprotein Accumulation and Modification** • ***Fatty streak formation*** An integrated view of experimental results in animals and study of human atherosclerosis suggests that the "fatty streak" represents the initial lesion of atherosclerosis (Fig. 241-1). The formation of these early lesions of atherosclerosis most often seems to arise from focal increases in the content of lipoproteins within regions of the intima (Fig. 241-1*B*). This accumulation of lipoprotein particles may not result simply from an increased permeability, or "leakiness," of the overlying endothelium. Rather, these lipoproteins may collect in the intima of arteries because they bind to constituents of the extracellular matrix, increasing the residence time of the lipid-rich particles within the arterial wall. Lipoproteins that accumulate in the extracellular space of the intima of arteries often associate with proteoglycan molecules of the arterial extracellular matrix. At sites of lesion formation, the balance of different matrix constituents may vary in important ways. Of the three major classes of proteoglycans, for example, a relative excess of heparan sulfate molecules in relation to keratan sulfate or chondroitin sulfate may promote the retention of lipoprotein particles by binding them and slowing their egress from nascent lesions.

Lipoprotein particles in the extracellular space of the intima, particularly those bound to matrix macromolecules, may undergo chemical modifications. Accumulating evidence supports a pathogenic role for such modifications of lipoproteins in atherogenesis. Two types of such alterations in lipoproteins bear particular interest in the context of understanding how risk factors actually promote atherogenesis: oxidation and nonenzymatic glycation.

Lipoprotein oxidation Lipoproteins sequestered from plasma antioxidants in the extracellular space of the intima may be particularly susceptible to oxidative modification. Oxidatively modified low-density lipoprotein (LDL), rather than being a defined homogenous entity, actually comprises a variable and incompletely defined mixture. Both the lipid and protein moieties of these particles can participate in oxidative modification. Modifications of the lipids may include formation of hydroperoxides, lysophospholipids, oxysterols, and aldehydic breakdown products of fatty acids. Recently recognized phospholipid oxidation products include palmitoyl-oxovaleroyl-glycero-phosphoryl choline (POVPC), palmitoyl-glutaroyl-glycero-phosphoryl choline (PGPC), and epoxyisoprostane E_2-glycero-phosphocholine (PEIPC). Modifications of the apoprotein moieties may include breaks in the peptide backbone as well as derivatization of certain amino acid residues. The side chain amino group of lysine may condense with components of the oxidized lipids (4-hydroxynonenal or malondialdehyde). A more recently recognized modification, ni-

trolled by systemic anticoagulation (heparin, 7000 to 10,000 units during the procedure to maintain an activated clotting time of 250 to 300 s), and antiplatelet therapy (aspirin, 325 mg/d starting at least 24 h before PCR and continued for at least 3 to 6 months after the procedure). If a coronary stent has been placed, aspirin is supplemented by a blocker of the platelet ADP receptor (ticlopidine or clopidogrel) to reduce the likelihood of stent thrombosis (see below). Newer potent intravenous antiplatelet agents (blockers of the platelet glycoprotein IIb/IIIa receptors) may reduce further the incidence of ischemic complications within 72 h of PCR, and are used prophylactically in what are perceived to be high-risk interventions or provisionally in interventions that have left behind an imperfect mechanical result (e.g., an unstented distal dissection).

Perforation of a coronary artery was an extremely rare complication of conventional balloon angioplasty but may occur in up to 1% of patients undergoing more aggressive atherectomy procedures (see below). Even small perforations of the distal vessel by the angioplasty guidewire may lead to significant hemopericardium requiring urgent pericardiocentesis in the setting of intense anticoagulant and antiplatelet therapy. Finally, catheter-based interventions are subject to all of the complications of diagnostic catheterization, including adverse reactions to iodinated contrast agents and groin hematoma. By and large, however, catheter-based coronary revascularization has reached the point of being a safe and effective alternative to surgical revascularization.

FOLLOW-UP After successful PCR of all "culprit" lesions, marked improvement or complete resolution of the presenting ischemic syndrome should be evident. In approximately 20% of patients, however, evidence of recurrent ischemia develops within 6 months, due to restenosis of the dilated segment. This restenosis appears to result from excessive local fibrointimal proliferation and vessel constriction, occurring in response to the local injury that is part of enlarging the stenotic lumen. When recurrent ischemia develops more than 6 months after PCR, it usually reflects progression of disease at another site, rather than restenosis. Whether due to restenosis or disease progression, most post-PCR problems can be treated by repeat PCR, so that only about 10% of patients require bypass surgery during the 5 years after a successful procedure. When a patient has provided evidence of severe obstructive coronary atherosclerosis requiring revascularization, either by bypass surgery or PCR, the opportunity to implement an aggressive program to reduce atherosclerotic risk factors and thereby slow the pace of development of new lesions should not be overlooked (Chap. 244).

NONBALLOON TECHNIQUES Conventional balloon angioplasty (PTCA) was the only catheter-based coronary revascularization technique that was widely available before 1990. Although it offered anatomic versatility and acceptable short- and long-term results, the difficulty of using this technique for certain anatomic lesion types (e.g., calcified eccentric, ostial, thrombus-containing, or bifurcation lesions) and the persistence of problems such as abrupt closure and restenosis fostered the development of a number of newer, nonballoon techniques that include stent placement and atherectomy. These treatments moved from clinical investigation to routine clinical practice during the early 1990s and now account for 70 to 80% of percutaneous coronary interventions. Used appropriately, these new techniques have improved the success, safety, and long-term results (restenosis rate) in most lesion types. Most of these procedures cost more than PTCA, but much of this cost can be recouped by the reduction in long-term expenses for the treatment of restenosis. Given these developments, stand-alone balloon angioplasty is now used in a minority of procedures (20% of all PCRs), although adjunctive balloon angioplasty is still routinely used to pre- or postdilate, before or after a newer interventional device.

STENTS Stents are metallic scaffolds that are inserted into a diseased vessel segment in their collapsed form and are then expanded (by balloon expansion, or by self-expansion after removal of a constraining membrane) to establish a normal-appearing vessel lu... Stents overcome two of the principal limitations of balloon d... tion—the tendency for elastic recoil of the vessel wall and local... section of the plaque. As such, stents provide a larger acute lumen than does conventional balloon angioplasty, which allows them to reduce the incidence of subsequent restenosis by roughly one-third (e.g., angiographic restenosis rates of 20% versus 33%, and clinical restenosis rates of 10% versus 16 to 20%). When in-stent restenosis does occur, it is almost never the result of stent crush but rather the consequence of excessive neointimal hyperplasia within the stent (Fig. 245-4). In-stent restenosis can be treated by atherectomy to remove the excess tissue (see below), balloon dilatation, and then local delivery of β or γ radiation to suppress neointimal regrowth.

Two balloon-expandable stent designs were approved by the Food and Drug Administration (FDA) in the early 1990s—a wire coil design for use in stabilizing actual or threatened abrupt closure and a slotted tube design for elective treatment of native coronary lesions. After their release, the efficacy of the slotted tube design was demonstrated in a variety of other circumstances, including restenotic lesions and saphenous vein grafts (Fig. 245-3). In the late 1990s, a number of second generation stent designs were developed that offer easier delivery to tortuous or distal lesions as well as a wider variety of sizes and lengths. The approval of these devices has allowed them to completely replace the first generation devices in clinical practice (Fig. 245-5). Still further refinements in stent coverings (to seal aneurysms or perforations) and coatings (to suppress stent thrombosis and in-stent proliferation) are in progress.

Early experience suggested that metallic stents were prone to thrombotic occlusion, either acute (<24 h) or subacute (1 to 14 days with a peak at 6 days), and that an aggressive anticoagulation regimen (aspirin, dipyridamole, and warfarin) was needed to prevent such thrombosis. This aggressive anticoagulant regimen reduced the incidence of stent thrombosis to ~3% but led to longer hospitalization and an increased incidence of local vascular complications at the femoral arterial entry site. Subsequent data suggested that many of these thrombotic complications were the result of incomplete stent expansion and that more attention to full initial deployment would allow the same stents to be used with only antiplatelet drugs (aspirin plus the platelet ADP-receptor blockers, ticlopidine or clopidogrel) with more

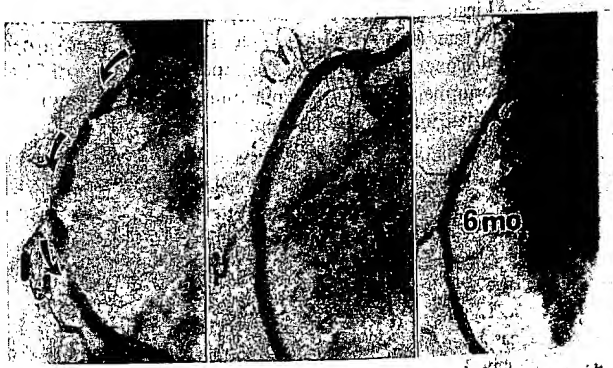

FIGURE 245-4 Short- and long-term results in a long lesion in the right coronary artery. *Left*: A long (~50 mm) area of disease (*arrows*) is present in the right coronary artery. *Right center*: Contrast injection after placement of two long second generation stents (25 and 35 mm long) shows excellent patency throughout the proximal- and mid-portions of the vessel. *Right*: Follow-up angiogram 6 months after stent placement shows mild lumen reduction throughout the stented segment due to neointimal hyperplasia within the stent (note the separation between the stent shadows and the contrast-filled lumen). Mild degrees of proliferative narrowing are benign and common within stents (particularly long stents such as this one). Had the degree of lumen reduction been greater and associated with recurrent symptoms or an abnormal exercise test, however, re-intervention would have been performed with a debulking technique (e.g., rotational atherectomy) followed by balloon angioplasty and possibly local radiation delivery (brachytherapy) to inhibit excessive tissue regrowth.

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Medical Dictionary

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Main Entry: **in·ti·ma**
Pronunciation: □int-□-m□
Function: *noun*
Inflected Form(s): *plural* **in·ti·mae** /-□m□, -□m□ /; *or* **in·ti·mas**
: the innermost coat of an organ (as a blood vessel) consisting usually of an endothelial layer backed by connective tissue and elastic tissue -- called also *tunica intima*
- **in·ti·mal** /-m□l/ *adjective*

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Pronunciation Key

\&\ as a and u in abut	\ch\ as ch in chin	\o\ as aw in law
\ᵊ\ as e in kitten	\e\ as e in bet	\oi\ as oy in boy
\&r\ as ur and er in further	\E\ as ea in easy	\th\ as th in thin
	\g\ as g in go	\th\ as th in the
\a\ as a in ash	\i\ as i in hit	\ü\ as oo in loot
\A\ as a in ace	\I\ as i in ice	\u\ as oo in foot
\ä\ as o in mop	\j\ as j in job	\y\ as y in yet
\au\ as ou in out	\[ng]\ as ng in sing	\zh\ as si in vision
	\O\ as o in go	

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